



## **NEW PLANT BASED AGENTS AS BIOAVAILABILITY / BIOEFFICACY ENHANCERS FOR DRUGS AND NUTRACEUTICALS**

### **Field of the invention.**

The present invention is directed to isolation/ preparation of an active molecule and/ or a fraction from the plant *Cuminum cyminum* which includes their isolation, purification and characterisation and methods of using such products to enhance bioavailability of drugs, natural products and essential nutraceuticals. The present invention is intended to enhance the bioavailability/ bioefficacy of drugs which are poorly bioavailable or given for a long period of time and are expensive and toxic. The present invention also relates to the use of bioavailability enhancers – also termed as bioenhancers or BE and methods of their preparation which include their isolation from a natural source and obtaining the final product in the form of a pure isolate and /or a fraction with all the components in a chemically characterized or their fingerprint profiled form.

### **Background of the invention**

There is a great interest and medical need for the improvement of bioavailability of a large number of drugs which are (a) poorly bioavailable, (b) given for long periods, and are (c) toxic and expensive. Maximizing oral bioavailability is therapeutically important because the extent of bioavailability directly influences plasma concentrations as well as therapeutic and toxic effects resulting after oral drug administration. Poorly bioavailable drugs remain sub-therapeutic because a major portion of a dose never reaches the plasma or exerts its pharmacological effect unless and until very large doses are given which may lead to serious side effects. Any significant improvement in bioavailability will result in lowering the dose or the dose frequency of that particular drug. Besides, inter-subject variability is inversely correlated with the extent of bioavailability. Therefore, low oral bioavailability leads to high variability and poor control of plasma concentration and pharmacodynamic effects. Inter-subject variability is particularly of concern for a drug with a narrow safety margin.

Incomplete oral bioavailability has various causes. These include poor dissolution or low aqueous solubility, poor intestinal membrane permeation, degradation of the drug in gastric or intestinal fluids and pre-systemic intestinal or hepatic metabolism. The normal practice

to offset some of these problems has been to increase the dosage as stated earlier which has the concerns of patients' non-compliance and toxicity.

Many therapeutic treatments are also accompanied by loss of essential nutraceuticals in the course of therapy. The present invention improves nutritional status by increasing bioavailability/ bioefficacy of various nutraceuticals also which include metals and vitamins.

### **Description of related art**

Several approaches have been adopted in the past to maximize oral bioavailability, such as (a) micronization, (b) polymorphic or crystal size and form selection, (c) solubilization of lesser soluble drugs by way of chemical modifications, complexation and use of co-solvents/ surfactants, (d) targeted delivery of drug at the site of action, (e) controlled drug delivery by film coating or use of polymeric matrices for sustained release of drugs, (f) prodrug approach, and (g) microencapsulation using liposomes.

However, based on clues from Ayurvedic literature, a new approach of increasing the bioavailability of drugs including poorly bioavailable drugs had been conceptualized at RRI Jammu. One of the groups of herbals which has been documented very frequently as essential part of about 70 % of Ayurvedic prescriptions, was noted to be 'Trikatu', that comprises the three acrids viz. long pepper, black pepper and dry ginger in equal proportions. A single major alkaloidal constituent from peppers (piperine) was found to be responsible for bioavailability enhancing effect. Influence of piperine was extensively studied on anti-TB drugs. It was determined that in combination with piperine the dose of rifampicin can be reduced by about 50% while retaining the therapeutic efficacy of this anti-TB drug at par with the standard dose (450 mg). Based on these findings several other reputed plants were evaluated for bioavailability/ bioefficacy enhancing activity. Polar and non-polar extracts of parts of a few plants viz., *Zingiber officinalis*, *Carum carvi* and *Cuminum cyminum* increased significantly (25 – 300 %) , the bioavailability of a number of classes of drugs, for example, but not limited to, antibiotics, antifungals, anti-virals, anticancer, cardiovascular, CNS, anti-inflammatory/anti-arthritic, anti-TB/antileprosy, anti-

histaminic/, corticosteroids, immunosppressants. Such extracts either in presence or absence of piperine have been found to be highly selective in their bioavailability/bioefficacy enhancing action.

#### **Brief description of the drawings**

Fig. 1 shows the chemical name and structure of the active molecule of the invention;

Fig. 2 shows an HPLC fingerprint of the active molecule; and

Fig. 3 sows an HPCL fingerprint of a fraction from the plant *Cuminum cyminum*.

#### **Description of the preferred embodiment**

The present invention is directed to isolation/ preparation of an active molecule and a fraction from the plant *Cuminum cyminum*. which includes their isolation, purification and characterisation and methods of using such products to enhance bioavailability of drugs, natural products and essential nutraceuticals. The products of the present invention viz., an active molecule and a fraction enhances bioavailability/ bioefficacy of certain drugs, natural products and essential nutraceuticals. The compound (Fig 1) though known has been for the first time reported to be useful as an effective bioavailability enhancer. The HPLC fingerprint of Fig. 2 was done on the following sample:

Sample	:	3',5-Dihydroxy flavone-7-O- $\beta$ -D-galacturonide-4'-O- $\beta$ -D-glucopyranoside
Concentration	:	0.0024 gm/10 mL H <sub>2</sub> O
Inj. Vol.	:	5 $\mu$ L
Column	:	RP-18, 5 $\mu$ m
Mobile Phase	:	2% acetic acid in H <sub>2</sub> O : ACN (83:17)
Flow rate	:	1 mL/min.

The HPLC fingerprint of Fig. 3 was done on the following sample:

Sample	:	Fraction
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Concentration : 0.0752 gm/10 mL H<sub>2</sub>O  
 Inj. Vol. : 30  $\mu$  L  
 Column : RP-18, 5  $\mu$  m  
 Mobile Phase : 2% acetic acid in H<sub>2</sub>O : ACN (83:17)  
 Flow rate : 1 mL/min.

Greenish yellow powder (H<sub>2</sub>O:EtOH), soluble in H<sub>2</sub>O, m.p. 270°C decompose.

UV  $\lambda_{\text{max.}}$  nm

MeOH	256.5, 267.5 sh, 350
NaOMe	265.5, 393, 5
AlCl <sub>3</sub>	273, 327.5 sh, 429.5

Physical and chemical data of as 3',5-Dihydroxy flavone-7-O- $\beta$ -D-galacturonide-4'-O- $\beta$ -D-glucopyranoside

Greenish yellow powder (H<sub>2</sub>O:EtOH), soluble in H<sub>2</sub>O, m.p. 270°C decompose.

UV  $\lambda_{\text{max.}}$  nm

MeOH	256.5, 267.5 sh, 350
NaOMe	265.5, 393, 5
AlCl <sub>3</sub>	273, 327.5 sh, 429.5
AlCl <sub>3</sub> / HCl	266, 358
NaOAc	261.5, 406.5
NaOAc/H <sub>3</sub> BO <sub>3</sub>	260, 374.5

<sup>1</sup>HNMR (DM SO-d6):

$\delta$  3.08-3.75 (m, 17H, sugar protons), 4.50 (d, 1H,  $J$ = 7.21 Hz, H-1<sup>'''</sup>), 5.21 (d, 1H,  $J$ = 6.82 Hz, H-1<sup>''</sup>), 6.42 (bs, 1H, H-6), 6.65 (bs, 1H, H-8), 6.81 (d, 1H,  $J$ = 8.42, H-5<sup>'</sup>), 7.09 (s, 1H, H-3), 7.35 (q, 1H,  $J$ = 8.42 and 1.8 Hz, H-6<sup>'</sup>), 7.80 (bs, 1H, H-2<sup>'</sup>).

<sup>13</sup>CNMR (H<sub>2</sub>O-CD<sub>3</sub>OD) :

$\delta$  165.36 (C-2), 104.01 (C-3), 183.19 (C-4), 160.87 (C-5), 99.41 (C-6), 163.09 (C-7), 96.31 (C-8), 157.65 (C-9), 106.50 (C-10), 122.36 (C-1'), 114.10 (C-2'), 145.37 (C-3'), 148.74 (C-4'), 116.81 (C-5'), 120.75 (C-6'), 101.21 (C-1''), 73.25 (C-2''), 77.23 (C-3''), 70.72 (C-4''), 76.89 (C-5''), 62.02 (C-6''), 103.39 (C-1'''), 75.02 (C-2''') and C-4'''), 77.71 (C-3''') 82.07 (C-5''') ,176.44 (C-6''').

On the basis of above data the compound has been identified as 3',5-Dihydroxy flavone-7-O- $\beta$ -D-galacturonide-4'-O- $\beta$ -D-glucopyranoside (Fig. 1).

The products of the invention act by any one or more than one of the following ways: (a) Promoting the absorption of drugs from GIT, (b) Inhibiting or reducing the rate of biotransformation of drugs in the liver or intestines, (c) Modifying the immune system in a way that the overall requirement of the drug is reduced substantially, (d) Increasing the penetration or the entry into the pathogens even where they become persistors within the macrophages such as for *Mycobacterium tuberculosis* and such others. This eventually ensures the enhanced killing of these organisms well secured within the places otherwise inaccessible to the active drug. (e) Inhibiting the capability of pathogens or abnormal tissue to reject the drug e.g., efflux mechanisms frequently encountered with anti-malarial, anti-cancer and anti-microbial drugs, (f) Modifying the signalling process between host and pathogen ensuring increased accessibility of the drugs to the pathogens, (g) Enhancing the binding of the drug with the receptors like proteins, DNA, RNA, etc., in the pathogen, thus potentiating and prolonging its effect leading to enhanced antibiotic activity against pathogens, (h) Besides above plausible modes of action, the bioenhancer agents may also be useful for promoting the transport of nutrients and the drugs across the blood brain barrier , which could be of immense help in the control of diseases like cerebral infections, epilepsy and other CNS problems.

Primarily, but not exclusively, the invention enhances the carrier mediated entry of drugs and also the passive diffusion and the active transport pathways in the tissue which are responsible for transporting physiological substances such as nutraceuticals to their target sites. As applicable to any mechanism of action the products of this invention contribute in a synergistic and /or additive manner so that most drugs and nutraceuticals in presence of the products described in the present art are more bioavailable as a result of one or more of these mechanisms. As a preferred embodiment, the active molecule and the fraction increase the plasma levels and bioefficacy of certain categories of drugs and nutraceuticals by 80 - 220 % over the effect that results from normal intake of therapeutic and nutraceutical products.

The ratio (w/w) of an effective bioenhancer (fraction / active molecule) in combination with a drug/ nutraceutical may vary in the range of 0.1 to 300 %.

The bioavailability of drugs and nutraceuticals is also relevant to animal health besides being important for humans. The invention therefore is also intended to be used in veterinary preparations.

**EXAMPLES:** The following examples are intended to demonstrate some of the preferred embodiments and in no way should be construed so as to limit the scope of the invention. Any person skilled in the art can design more formulations, which may be considered as part of the present invention.

**Example 1:**

*Cuminum cyminum* seeds (0.5 kg) were ground to a coarse powder and then extracted with deionised water at  $98\pm 1^{\circ}\text{C}$  for 2 hrs. Extraction process was repeated four times using total of 3.1 litres water (1 x 1 litre + 3 x 0.7 Litre, four extractions). All the four extracts were pooled. The pooled extract was centrifuged, followed by vacuum filtration through a celite bed. The clear filtrate was lyophilized to get greenish yellow amorphous powder (yield 88 gm, 17. 6 %). The dry extract was dissolved in deionised water (500 mL) and

partitioned between n-BuOH (6 x 500 mL) and H<sub>2</sub>O. The n-BuOH extract was concentrated on a rotavapour under reduced pressure at 65°C (residue 11.0 gm). n-BuOH free aqueous extract was freeze dried (residue 75.0 gm) and subjected to adsorption chromatography. Aqueous extract residue was dissolved in minimum quantity of H<sub>2</sub>O and adsorbed on SiO<sub>2</sub> gel, 60-120 mesh (150 gm). Solvent was completely removed to get free flowing material. A glass column of 1.5 inch dia was packed with 100 gm SiO<sub>2</sub> gel, 60-120 mesh in EtOAc. The adsorbed material was charged in the column over the packed SiO<sub>2</sub> gel. The column was eluted with EtOAc and then with EtOH by gradually increasing the %age of H<sub>2</sub>O in EtOH. In all 420 fractions of 70 mL each were collected and pooled on the basis of TLC pattern using BuOH (B) : AcOH (A) : H<sub>2</sub>O (W) (4:1:5) as developing solvent. Spots were visualized by spraying with freshly prepared Borinate-PEG solution [ 1% solution of 2-aminoethyl diphenylborinate in MeOH and 5% solution of polyethylene glycol 4000 in EtOH ( mixed 1:1 v/v before spraying)]. Fraction no. 81-167 (eluted in EtOH and 10% H<sub>2</sub>O in EtOH) showed same TLC pattern. These fractions were pooled, dried and then dissolved in minimum quantity of water. Crystallisation was carried out by the addition of EtOH in small portions, supernatant was drained off and residue was washed with aq. EtOH. Residue was repeatedly crystallized from H<sub>2</sub>O : EtOH. A yellow powder (70 mg) soluble in H<sub>2</sub>O was thus obtained. Compound Rf 0.28 solvent system B : A : W (4:1:5) was identified as 3',5 -dihydroxy flavone 7-O-β-D-galacturonide-4'-O-β-D-glucopyranoside.

#### Example 2

*Cuminum cyminum* seeds (0.5 kg) were ground to a coarse powder. The powder was soaked in 50% aqueous ethanol (1.0 L) for 16 hrs. The marc was extracted three times more under same conditions using 0.7 L of extraction solvent each time. The pooled extract was clarified by vacuum filtration through a celite bed. The extract thus obtained was concentrated at 60 ± 2°C on a rotavapour. The EtOH free extract was lyophilized to get a greenish yellow powder (88 gm, 17.60%). 80 gm of the extract was extracted by heating on a steam bath respectively with

1.	CHCl <sub>3</sub>	( 2 X 200 mL)
2.	10% EtOH in CHCl <sub>3</sub>	( 1x 200)
3.	20% EtOH in CHCl <sub>3</sub>	( 1x 200 mL )
4.	30% EtOH in CHCl <sub>3</sub>	( 1x 200 mL)
5.	40% EtOH in CHCl <sub>3</sub>	( 1x 200 mL)
6.	50% EtOH in CHCl <sub>3</sub>	( 1x 200 mL)
7.	60% EtOH in CHCl <sub>3</sub>	( 1x 200 mL)
8.	70% EtOH in CHCl <sub>3</sub>	( 1x 200 mL)
9.	EtOH	(6 x 200 mL)
10.	EtOH + 10% H <sub>2</sub> O	(1 x 200 mL)

The insoluble residue left after extraction with 10% water in EtOH was then extracted at room temperature with EtOH + 20% H<sub>2</sub>O (3 x 500 mL). The left over fraction (25 gm) was subjected to adsorption chromatography. It was adsorbed on silica gel (60-120 mesh 70 gm). Solvent was completely removed to get free flowing material. A glass column of 1.5 inch dia was packed with 70 gm SiO<sub>2</sub> gel 60-120 mesh in EtOH. The adsorbed extract was charged in the column. The column was eluted with EtOH by gradually increasing the %age of H<sub>2</sub>O. In all 94 fractions of 70 mL each were collected and pooled on the basis of TLC pattern using B:A:W (4:1:5) as developing solvent. Spots were visualized by spraying the TLC plate with Borinate PEG spray reagent. Fractions 56-80 homogeneous on TLC were pooled, dried and charged on a Sephadex LH-20 column. Column was eluted with water then with EtOH to produce two fractions of 200 and 500 mL respectively. The first fraction was purified repeatedly (three times) on Sephadex LH-20 column. TLC homogeneous fractions containing target compound were pooled and residue was repeatedly crystallized from H<sub>2</sub>O : EtOH. A yellow powder (50 mg) soluble in water was obtained. Compound Rf 0.28 , Solvent system : B : A : W (4 : 1 : 5) was identified 3',5 - dihydroxyflavone 7-O- $\beta$ -D-galacturonide-4'-O- $\beta$ -D-glucopyranoside.

### **Example 3**

*Cuminum cyminum* seeds (100 gm) were ground to a coarse powder. Coarse powder was extracted with deionised water at  $98 \pm 1^{\circ}\text{C}$  for 2 hrs. Extraction process was repeated four times using total water (200 +3x 100 mL four extractions). All the four extracts were centrifuged, followed by vacuum filtration through celite bed. The clear filtrate was lyophilized to get a greenish yellow amorphous powder (yield 17.0 gm , 17%). Aqueous extract residue was dissolved in deionised water (100 mL) and partitioned between n-BuOH (6 x 100 mL) and H<sub>2</sub>O . The n-BuOH extract was concentrated on a rotavapour under reduced pressure at  $65^{\circ}\text{C}$  (residue 2.3 gm) . n-BuOH free aqueous extract was freeze dried (residue 13.9 gm). The aqueous residue was dissolved in HPLC grade H<sub>2</sub>O (15 mg/mL) and subjected to further purification by preparative HPLC under following conditions:

Column	: RP-18, length 10 cmx2 cartridge with guard column
Column dia	: 1.5 cm
Sample concentration	: 15 mg/mL
Injection volume	: 4 mL
Mobile phase	: CH <sub>3</sub> CN: H <sub>2</sub> O (1:9)
Flow rate	: 10 mL/min.
$\lambda_{\text{max}}$	: 271 nm
Run Time	: 50 minutes

Pooled target fraction was concentrated under reduced pressure and crystallized from H<sub>2</sub>O : EtOH to afford a yellow powder 110 mg , compound R<sub>f</sub> 0.28 , solvent system B : A : W (4 : 1 : 5) and was identified as 3',5-dihydroxy flavone 7-O- $\beta$ -D-galacturonide-4'-O- $\beta$ -D-glucopyranoside.

### **Example 4 :**

*Cuminum cyminum* seeds (0.5 kg) were ground to a coarse powder. Coarse powder was defatted with pet. ether 60-80 (1.0 litre) by Soxhlet extraction for 8 hrs. Pet. ether extract was discarded. The marc was dried and then extracted with EtOH (1.0 litre) by Soxhlet extraction for 16 hrs. The EtOH extract was also discarded. The marc was then extracted with 50% aqueous EtOH at room temperature for 16 hrs each time (Total solvent used 1 litre + 4 x 0.5 litre, five extractions). All the five extracts were pooled, concentrated on a rotavapour (residue 67 gm). This residue was dissolved in a minimum quantity of water and adsorbed on silica gel 60-120 mesh (125 gm). A glass column of 1.5 inch dia was packed with silica gel 60-120 mesh (100 gm) in EtOH. The adsorbed extract was charged in the column. Elution was carried out with solvents by gradually increasing the %age of H<sub>2</sub>O. Each fraction of 50 mL was collected. The fractions (148-190) eluted in 10% H<sub>2</sub>O in EtOH were pooled and subjected to further purification by preparative HPLC using following conditions.

Column	:RP-18, length 10 cmx2 cartridge with guard column
Column dia	:2.5 cm
Sample concentration	:15 mg/mL
Injection volume	: 4 mL
Mobile phase	:CH <sub>3</sub> CN: H <sub>2</sub> O (1:9)
Flow rate	:10 mL/min.
$\lambda_{max}$	:271 nm
Run Time	:50 minutes

Pooled target fraction was concentrated under reduced pressure and crystallized from H<sub>2</sub>O : EtOH to afford a yellow powder (60 mg) soluble in water, compound R<sub>f</sub> 0.28, solvent system B : A : W (4 : 1 : 5) and was identified as 3',5 -dihydroxyflavone 7-O- $\beta$ -D-galacturonide-4'-O- $\beta$ -D-glucopyranoside.

**EXAMPLE 5.** List of drugs cited as some of the examples for the purpose of the present invention.

	Categories	Drugs
I	<b>Antibiotics</b>	<b>Fluoroquinolones:</b> Cipro-, Nor-, P-, and 0-floxacins <b>Macrolides:</b> Erythro-, Roxithro-, and Azithromycin <b>Cephalosporins:</b> Cefixime, Cefalexin, Cefadroxil, Cefatrioxone <b>Penicillins:</b> moxycillin, Cloxacillin <b>Aminoglycosides:</b> Amikacin, Kanamycin
II.	<b>Antifungal</b>	Fluconazole, Amphotericin B, Ketoconazole
III.	<b>Anti-viral</b>	Acyclovir, Zidovudine
IV.	<b>Anti-cancer</b>	Methotrexate, 5-Fluorouracil, Doxorubicin Cisplatin
V.	<b>Cardiovascular</b>	Amlodipin, Lisinopril, Atenolol
VI.	<b>CNS</b>	Alprazolam, Haloperidol
VI.	<b>Anti-inflammatory/ antiarthritic (NSAID)</b>	Diclofenac Piroxicam, Nimesulide, Rofecoxib
VII.	<b>Anti-TB/ Antileprosy</b>	Rifampicin Ethionamide, Isoniazid, Cycloserine, Dapsone, Pyrazinamide, Ethambutol
VIII.	<b>Anti histamines/ respiratory disorders</b>	Salbutamol, Theophylline, Bromhexine, Loratadine
IX.	<b>Corticosteroids</b>	Prednisolone, Dexamethasone, Betamethasone
X.	<b>Immunosuppressants</b>	Cyclosporin A, Tacrolimus Mycophenolate mofetil
XI.	<b>Antiulcer</b>	Ranitidine, Cimetidine, Omeprazole

**EXAMPLE 5 (i): Antibiotics:****(a) Fluroquinolones**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Ciprofloxacin	65	130
P- floxacin	55	137
O-floxacin	70	103
Norfloxacin	45	55

**(b) Macrolides**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Erythromycin	70	80
Roxythromycin	65	105
Azithromycin	82	115

**(c) Cephalosporins**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Cefalexin	70	105
Cefadroxil	85	120
Cefatrioxone	75	100
Cefixime	nil	Nil

**(d) Penicillins**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Amoxycillin	68	105
Cloxacillin	77	105

**(e) Aminoglycosides:**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Amikacin	76	87
Kanamycin	Nil	35

**5 (ii) Antifungal**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Fluconazole	110	105
Amphotericin B	95	90
Ketoconazole	77	85

**5 (iii) Anti-viral**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Acyclovir	89	110
Zidovudine	120	135

**5.(iv) CNS drugs:**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Alprazolam	70	75
Haloperidol	72	60

**5. (v) Anti-cancer**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Methotrexate	95	140
5-Fluorouracil	110	240
Doxorubicin	78	90
Cisplatin	65	95

**5. (vi) Cardiovascular:**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Amlodipine	80	130
Lisinopril	Nil	Nil
Atenolol	75	110
Propranolol	85	140

**5. (vii) Anti-inflammatory/ antiarthritic:**

Drug	% Enhancement in bioavailability

	Active molecule	Fraction
Diclofenac	105	125
Piroxicam	76	100
Nimesulide	90	115
Rofecoxib	43	70

**5. (viii) Anti-TB/ Antileprosy drugs:**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Rifampicin	90	170
Isoniazid	Nil	30
Pyrazinamide	Nil	Nil
Ethambutol	Nil	Nil
Dapsone	67	93
Ethionamide	120	110
Cycloserine	85	110

**5.(ix) Anti-histamines/respiratory disorders:**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Salbutamol	98	75
Theophylline	75	95
Bromhexine	Nil	35
Loratadine	62	45

**5. (x) Corticosteroids:**

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction

Prednisolone	46	57
Dexamethasone	67	60
Betamethasone	65	50

5. (xi) Immunosuppressants:

Drug	% Enhancement in bioavailability	
	Active molecule	Fraction
Cyclosporin A	135	170
Tacrolimus	90	110
Mycophenolate Mofeit	Nil	Nil

5. (xii) Anti-ulcer

Drug	% Enhancement in bioavailability.	
	Active molecule	Fraction
Ranitidine	95	95
Cimetidine	76	70
Omeprazole	72	87

**EXAMPLE 6: Herbal formulations:**

Drug	%Enhancement in bioavailability/ bioefficacy	
	Active molecule	Fraction
<i>Echinacea</i>	77	147
<i>Tinospora cordifolia</i>	102	185
<i>Picrorrhiza kurroa</i>	68	180
<i>Aegle marmelos</i>	Nil	Nil
<i>Andrographis paniculata</i>	Nil	190
<i>Emblica ribes</i>	67	90

<i>Asparagus racemosus</i>	78	145
<i>Terminalia chebula</i>	45	85
<i>Withania somnifera</i>	Nil	Nil
<i>Centella asiatica</i>	82	60

### C. Nutraceuticals

	Category
I.	Vitamins Vitamin A Vitamin E Vit.B1 Vit. B6 Vit B12 Vit. C Folic acid
II	Antioxidants β-Carotene Silymarin Selenium Lycopene Ellagiogallotannins
III	Natural herbal products Curcumin Boswellic acids Rutin
IV	Essential nutritional components Methionine Lysine Leucine

	Valine
	Isoleucine
	Zinc
	Calcium
	Glucose
	Potassium
	Copper
	Iron